

PRODUCT MONOGRAPH

IOPIDINE® 1%

Apraclonidine Hydrochloride Ophthalmic Solution, USP

1% Apraclonidine (as base)

Controls Postsurgical Intraocular Pressure

IOPIDINE® 0.5%

Apraclonidine Hydrochloride Ophthalmic Solution, USP

0.5% Apraclonidine (as base)

Glaucoma Therapy

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Glaucoma Therapy

CLINICAL PHARMACOLOGY

Apraclonidine is a relatively selective alpha adrenergic agonist and does not have significant membrane stabilizing (local anesthetic) activity. When instilled into the eye, Apraclonidine Hydrochloride Ophthalmic Solution has the action of reducing intraocular pressure. The precise mechanism of the ocular hypotensive action of Apraclonidine Hydrochloride Ophthalmic Solution is not completely established at this time. Aqueous fluorophotometry studies in man suggest that apraclonidine's predominant action may be related to a reduction of aqueous formation.

Apraclonidine is a partial agonist for alpha 1 and alpha 2 adrenergic receptors. The affinity of apraclonidine for alpha 2 receptors, as measured by competitive radioligand binding studies, is much higher than its affinity towards alpha 1 receptors.

The onset of action with Apraclonidine Hydrochloride Ophthalmic Solution can usually be noted within one hour and the maximum intraocular pressure reduction usually occurs three to five hours after application of a single dose.

INDICATIONS AND CLINICAL USES

IOPIDINE 1% (Apraclonidine Hydrochloride Ophthalmic Solution) is indicated to control or prevent postsurgical elevations in intraocular pressure that occur in patients after anterior segment laser ophthalmic surgery including argon laser trabeculoplasty, argon laser iridotomy and neodymium:yttrium aluminum garnet (Nd:YAG) laser posterior capsulotomy.

IOPIDINE 0.5% (Apraclonidine Hydrochloride Ophthalmic Solution) is indicated for adjunctive use in lowering intraocular pressure and may be used as a short-term therapy in glaucoma patients on maximally tolerated medical therapy who require an additional IOP reduction.

The largest body of clinical data regarding the efficacy of apraclonidine as an adjunctive drug has been obtained in patients using timolol as the primary therapy. However, apraclonidine has also been found effective in combination with topical betaxolol, carbachol, dipivefrin, echothiophate, epinephrine, levobunolol and pilocarpine and systemic acetazolamide and methazolamide.

The addition of IOPIDINE 0.5% Ophthalmic Solution to patients already using two aqueous suppressing drugs (i.e. beta-blocker plus carbonic anhydrase inhibitor) as part of their maximally tolerated medical therapy may not provide much additional benefit. Since IOPIDINE 0.5% Ophthalmic Solution is an aqueous suppressing drug, the addition of a third aqueous suppressant may not significantly reduce IOP.

CONTRAINDICATIONS

Hypersensitivity to any other component of this medication, or to clonidine. Also contraindicated in patients receiving monoamine oxidase inhibitors.

WARNINGS

Since Apraclonidine Ophthalmic Solution is a potent depressor of intraocular pressure, patients may develop exaggerated reductions in intraocular pressure and should be closely monitored.

Although the acute administration of two drops of IOPIDINE 1% (Apraclonidine Hydrochloride) Ophthalmic Solution has minimal effect on heart rate or blood pressure in clinical studies evaluating patients undergoing anterior segment laser surgery, or glaucoma, the preclinical pharmacology profile of this drug suggests that caution should be observed in treating patients with severe cardiovascular disease, including hypertension.

The possibility of a vasovagal attack occurring during laser surgery should be considered and caution used in patients with history of such episodes.

Use of IOPIDINE 0.5% (Apraclonidine Hydrochloride) Ophthalmic Solution can lead to an allergic-like reaction characterized wholly or in part by the symptoms of hyperemia, pruritus, discomfort, tearing, foreign body sensation, and edema of the lids and conjunctiva. If ocular allergic-like symptoms occur, IOPIDINE 0.5% Ophthalmic Solution therapy should be discontinued. The allergic-like reaction associated with apraclonidine use may be masked by seasonal allergic conjunctivitis.

NOT FOR INJECTION. Topical ophthalmic use only.

PRECAUTIONS

General: (Glaucoma Therapy)

Although the topical use of IOPIDINE 0.5% (Apraclonidine Hydrochloride) Ophthalmic Solution has not been studied in renal failure patients, structurally related clonidine undergoes a significant increase in half-life in patients with severe renal impairment. Close monitoring of patients with impaired renal function is advised if they are candidates for topical IOPIDINE 0.5% solution therapy. Close monitoring of patients with impaired liver function is also advised as the systemic dosage form of clonidine is partly metabolized in the liver.

IOPIDINE 0.5% Ophthalmic Solution should be used with caution in patients with coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, Raynaud's disease, or thromboangitis obliterans. Caution and monitoring of depressed patients are advised since Apraclonidine has been rarely associated with depression.

IOPIDINE 0.5% Ophthalmic Solution can cause dizziness and somnolence. Patients who engage in hazardous activities requiring mental alertness should be warned of the potential for a decrease in mental alertness while using IOPIDINE 0.5% Solution.

Drug Interactions:

No specific drug interactions with topical glaucoma drugs (betaxolol, carbachol, dipivefrin, echothiophate, epinephrine, levobunolol, pilocarpine, timolol) or systemic medications (acetazolamide, methazolamide) were identified in clinical studies of IOPIDINE 0.5% (Apraclonidine Hydrochloride) Ophthalmic Solution. The possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, anesthetics) should be borne in mind. Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with Apraclonidine can lead to a reduction in IOP lowering effect. No data on the level of circulating catecholamines after Apraclonidine withdrawal are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Since Apraclonidine may reduce pulse and blood pressure, caution in using drugs such as beta-blockers (ophthalmic and systemic), antihypertensives, and cardiac glycosides is advised. Patients using cardiovascular drugs concurrently with Apraclonidine should have pulse and blood pressures frequently monitored. Caution should be exercised with simultaneous use of clonidine and other similar pharmacologic agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a series of five *in vitro* cell assays and one *in vivo*, apraclonidine was nonmutagenic

There was no significant increase in tumour incidence or type following two years of oral administration of apraclonidine HCl to rats at dose levels 20 times the maximum recommended human dose or in mice at dose levels 12 times the maximum recommended human dose.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses 5 to 10 times the maximum recommended human dose.

Pregnancy:

There are no adequate and well controlled studies in pregnant women. IOPIDINE (Apraclonidine Hydrochloride) Ophthalmic Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenicity studies with Apraclonidine HCl in rabbits and rats at doses up to 3.0 mg/kg/day in rabbits (60 times the maximum recommended human dose) and 0.3 mg/kg/day in rats (6 times the maximum recommended human dose) showed no evidence of fetal malformations, although embryotoxicity was evident at the high dose level in the rabbit study. Dose related maternal toxicity was evident in both the rat and rabbit studies.

Nursing Mothers:

It is not known if topically applied IOPIDINE (Apraclonidine Hydrochloride) Ophthalmic Solution is excreted in human milk. However, systemic clonidine can be found in mother's milk, and a decision should be made whether to discontinue IOPIDINE 0.5% Ophthalmic Solution use in nursing women or continue therapy, taking into account the importance of the drug to the mother. For surgical use, a decision should be considered to discontinue nursing temporarily for the one day IOPIDINE 1% solution is used.

Pediatric Use:

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Surgical Use:

The following adverse events were reported in association with the use of IOPIDINE 1% (Apraclonidine Hydrochloride) Ophthalmic Solution in laser surgery: upper lid elevation (1.3%), conjunctival blanching (0.4%) and mydriasis (0.4%).

Glaucoma Therapy:

Use of IOPIDINE 0.5% (Apraclonidine Hydrochloride) Ophthalmic Solution can lead to an allergic-like reaction characterized wholly or in part by the symptoms of hyperemia, pruritus, discomfort, tearing, foreign body sensation, and edema of the lids and conjunctiva. If ocular allergic-like symptoms occur, therapy should be discontinued.

The overall discontinuation rate in clinical studies with IOPIDINE 0.5% Ophthalmic Solution was 16%. The most commonly reported events leading to discontinuation included (in decreasing order of frequency) hyperemia, pruritus, discomfort, tearing, dry mouth, lid edema, and foreign body sensation.

The following adverse reactions (incidence) were reported in clinical studies of IOPIDINE 0.5% Ophthalmic Solution as being related to therapy:

Ocular

Hyperemia (11.9%), pruritus (11.3%), discomfort (7.2%), tearing (4.8%), foreign body sensation (2.7%), lid edema (2.4%), dry eye (2.1%), blurred vision (1.8%), blanching (1.5%), conjunctivitis (1.5%), lid margin crusting (1.2%), conjunctival edema (0.9%), discharge (0.9%), abnormal vision (0.9%), pain (0.6%), lid disorder (0.6%), edema (0.6%), lid erythema (0.6%), irritation (0.3%), keratitis (0.3%), blepharitis (0.3%), blepharoconjunctivitis (0.3%), photophobia (0.3%), conjunctival follicles (0.3%), scleritis (0.3%), keratopathy (0.3%), lid scales (0.3%), corneal infiltrate (0.3%), corneal staining (0.3%).

Body As A Whole

Headache (2.7%), asthenia (2.1%), chest pain (0.6%), abnormal coordination (0.3%), malaise (0.3%).

Cardiovascular

Peripheral edema (0.3%), arrhythmia. Although no reports of bradycardia related to Apraclonidine Hydrochloride Ophthalmic Solution 0.5% were available from clinical studies, the possibility of its occurrence based on Apraclonidine's alpha 2 agonist effect should be considered.

Central Nervous System

Somnolence (1.2%), dizziness (1.2%), depression (0.6%), nervousness (0.6%), insomnia (0.3%), paresthesia (0.3%).

Digestive System

Dry mouth (12.8%), constipation (1.5%), nausea (0.6%).

Musculoskeletal system

Myalgia (0.3%).

Respiratory System

Dry nose (3.3%), rhinitis (1.2%), dyspnea (0.3%), pharyngitis (0.3%).

Skin

Contact dermatitis (0.3%), dermatitis (0.3%).

Special Senses

Taste perversion (3.6%), parosmia (0.3%).

This listing is presented below and lists treatment-related adverse reactions which occurred at an incidence rate of 2.0% or more during placebo-controlled clinical studies of IOPIDINE 0.5% Ophthalmic Solution.

Coded Adverse Event	SINGLE THERAPY N=183		ADJUNCTIVE + MAXIMAL THERAPY N=152		PLACEBO N=160	
	N	%	N	%	N	%
Ocular						
Pruritus	24	13.1	14	9.2	1	0.6
Discomfort	19	10.4	5	3.3	7	4.4
Hyperemia	15	8.2	25	16.4	5	3.1
Tearing	11	6.0	5	3.3	1	0.6
Dry Eye	6	3.3	1	0.7	1	0.6
Foreign Body Sensation	5	2.7	4	2.6	1	0.6
Lid Edema	5	2.7	3	2.0	0	
Blanching	5	2.7	0		1	0.6
Blurred Vision	2	1.1	4	2.6	1	0.6
Conjunctivitis	2	1.1	3	2.0	0	
Nonocular						
<u>Body as a Whole</u> Headache	8	4.4	1	0.7	0	
Asthenia	7	3.8	0		3	1.9
<u>Central Nervous System</u> Somnolence	4	2.2	0		1	0.6
Dizziness	1	0.5	3	2.0	0	
<u>Digestive</u> Dry Mouth	39	21.3	4	2.6	16	10.0
Constipation	5	2.7	0		0	
<u>Respiratory</u> Dry Nose	11	6.0	0		1	0.6
Rhinitis	4	2.2	0		0	
<u>Special Senses</u> Taste Perversion	10	5.5	2	1.3	2	1.3

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdose is unlikely with topical ocular instillation, as the volume of exposure is limited by the capacity of the cul-de-sac. The small volume packaging and unique design of the DROPTAINER® limit the potential for accidental overdosage by ingestion. Signs of toxicity of apraclonidine in animals include lethargy, decreased activity, loss of appetite, hypothermia, decreased GI motility and constipation. Following oral administration of apraclonidine to monkeys, plasma levels 100 times greater than those seen in human plasma level studies were associated with moderate signs of toxicity, including lethargy, hypoactivity, and loss of appetite; no significant target organ toxicities were found. Acute oral toxicity studies in rats and mice resulted in LD₅₀ values of 64 and 5 mg/kg, respectively. While higher doses usually caused deaths within 24 hours, lower doses often resulted in delayed deaths.

While no instances of human ingestion of IOPIDINE (Apraclonidine Hydrochloride) Ophthalmic Solution are known, overdose with the oral form of clonidine has been reported to cause hypotension, transient hypertension, asthenia, vomiting, irritability, diminished or absent reflexes, lethargy, somnolence, sedation or coma, pallor, hypothermia, bradycardia, conduction defects, arrhythmias, dryness of the mouth, miosis, apnea, respiratory depression, hypoventilation, and seizure.

Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained. Gastric lavage, IV fluids, atropine, dopamine, tolazoline, furosemide and diazoxide have been reported to be useful in treating the systemic symptoms associated with oral clonidine overdose. Hemodialysis is of limited value, since a maximum of 5% of circulating drug is removed.

DOSAGE AND ADMINISTRATION

One drop of IOPIDINE 1% (Apraclonidine Hydrochloride Ophthalmic Solution) should be instilled in the scheduled operative eye one hour before initiating anterior segment laser surgery and a second drop should be instilled in the same eye immediately upon completion of the laser surgical procedure. Use a separate container for each single drop dose and discard each container after use.

One to two drops of IOPIDINE 0.5% (Apraclonidine Hydrochloride Ophthalmic Solution) should be instilled in the affected eye(s) two or three times daily. Since IOPIDINE 0.5% Ophthalmic Solution will be used with other ocular glaucoma therapies, an approximate 5 minute interval between instillation of each medication should be practised to prevent washout of the previous dose.

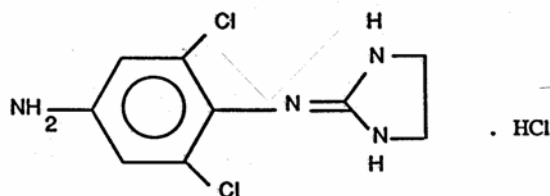
NOT FOR INJECTION INTO THE EYE. NOT FOR ORAL INGESTION.

PHARMACEUTICAL INFORMATION**CHEMISTRY:****Tradename:** IOPIDINE®**Drug Substance:**

Proper Name: Apraclonidine Hydrochloride

Chemical Name: 2-[(4-Amino-2,6-dichlorophenyl)imino]imidazolidine monohydrochloride

Structural Formula:

Empirical Formula: C₉H₁₀Cl₂N₄•HCl

Molecular Weight: 281.6

Description: Apraclonidine Hydrochloride is a white to off-white powder and is highly soluble in water.

Composition:

IOPIDINE 1% (Apraclonidine Hydrochloride Ophthalmic Solution) is a sterile isotonic aqueous solution containing apraclonidine hydrochloride 1.15% equivalent to 1% apraclonidine base with benzalkonium chloride 0.01% (as preservative), sodium chloride, sodium acetate, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

IOPIDINE 0.5% (Apraclonidine Hydrochloride Ophthalmic Solution) is a sterile isotonic aqueous solution containing apraclonidine hydrochloride 0.575% equivalent to 0.5% apraclonidine base with benzalkonium chloride 0.01% (as preservative), sodium chloride, sodium acetate, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

Stability and Storage Recommendations:

Store between 2-30°C (36 - 86°F). Do not freeze. Protect from light.

AVAILABILITY

^{Pr} IOPIDINE (Apraclonidine Hydrochloride Ophthalmic Solution) 1% apraclonidine as base, is a sterile isotonic aqueous solution containing apraclonidine hydrochloride. Supplied as follows: 0.1 mL in plastic ophthalmic dispensers, packaged two per pouch. These dispensers are enclosed in a foil overwrap as an added barrier to evaporation.

^{Pr} IOPIDINE (Apraclonidine Hydrochloride Ophthalmic Solution) 0.5% apraclonidine as base, is a sterile isotonic aqueous solution containing apraclonidine hydrochloride. Supplied in a 5 mL or 10 mL plastic DROP-TAINER® dispenser.

Apraclonidine is a Schedule F (prescription) drug.

PHARMACOLOGY

Human Pharmacology:

Pharmacodynamics:

Apraclonidine is a relatively selective alpha-2 adrenergic agonist and does not have significant membrane stabilizing (local anesthetic) activity. When instilled in the eye, IOPIDINE (Apraclonidine Hydrochloride Ophthalmic Solution), has the action of reducing elevated, as well as normal, intraocular pressure, whether or not accompanied by glaucoma.

Aqueous fluorophotometry studies demonstrate that Apraclonidine's predominant mechanism of action is reduction of aqueous flow via stimulation of the alpha-adrenergic system. Unlike beta-blockers and epinephrine, Apraclonidine reduces aqueous flow during the day and also at night during sleep. Apraclonidine's mechanism of action may account for the additional IOP reductions observed after instillation of Apraclonidine Ophthalmic Solution in patients receiving a beta-blocker or receiving maximally tolerated medical therapy.

Laser Surgery Therapy

Optic nerve head damage and visual field loss may result from an acute elevation in intraocular pressure that can occur after surgical procedures. Elevated intraocular pressure, whether acute or chronic in duration, is a major risk factor in the pathogenesis of visual field loss. The higher the peak or spike of intraocular pressure, the greater the likelihood of visual field loss and optic nerve damage especially in patients with previously compromised optic nerves.

Controlled clinical studies of patients requiring argon laser trabeculoplasty, argon laser iridotomy or Nd:YAG laser posterior capsulotomy showed that IOPIDINE 1% Ophthalmic Solution controlled or prevented the postsurgical intraocular pressure rise typically observed in patients after undergoing those procedures. After surgery, the mean intraocular pressure was 1.9 to 4.0 mm Hg below the corresponding presurgical baseline pressure before IOPIDINE 1% Ophthalmic solution treatment.

With placebo treatment, postsurgical pressures were 2.5 to 8.4 mm Hg higher than their corresponding presurgical baselines. Overall, only 2% of patients treated with IOPIDINE 1% Ophthalmic Solution had severe intraocular pressure elevations (spikes \geq 10 mm Hg) during the first three hours after laser surgery, whereas 23% of placebo-treated patients responded with severe pressure spikes (Table 1). Of the patients that experienced a pressure spike after surgery, the peak intraocular pressure was above the 30 mm Hg in most patients (Table 2) and was above 50 mm Hg in seven placebo-treated patients and one IOPIDINE 1% Ophthalmic Solution-treated patient.

Glaucoma Therapy:

Dose-response and comparative studies (0.125% - 1.0% apraclonidine) demonstrate that 0.5% apraclonidine is at the top of the dose/response IOP reduction curve. Based upon the dose response and efficacy studies, and the incidence of ocular allergic and systemic side effects (see Precautions), IOPIDINE 0.5% (Apraclonidine Hydrochloride) Ophthalmic Solution is recommended for short term use in glaucoma patients on maximally tolerated medical therapy who require an additional IOP reduction.

The utility of IOPIDINE 0.5% Ophthalmic Solution is most apparent for those glaucoma patients on maximally tolerated medical therapy. In such patients IOPIDINE 0.5% Ophthalmic Solution provided further IOP reductions of 2.1 to 3.2 mmHg for three months, even when patients were using a beta-blocker, epinephrine, pilocarpine, and oral carbonic anhydrase inhibitors, and had undergone laser trabeculoplasty. Among those patients on maximally tolerated medical therapy whose IOP remained uncontrolled at 22 mmHg or greater, IOPIDINE 0.5% Ophthalmic Solution was particularly effective, providing an additional IOP reduction of 3.7 to 5.0 mmHg. Filtration surgery was performed in about 15% of patients due to treatment failure; the average therapy time before surgery was 4.3 months. An additional 19.8% of patients were discontinued due to adverse events, primarily allergic-like reactions. Thus, in approximately two-thirds of the patients, IOPIDINE 0.5% Ophthalmic Solution provided substantial control of glaucoma.

Adjunctive therapy studies in glaucoma patients demonstrated that IOPIDINE 0.5% Ophthalmic Solution dosed BID for 90 days in patients receiving 0.5% Timolol, effectively lowered IOP by an additional 2.5 to 5.0 mmHg. The additional IOP reduction with Apraclonidine is more pronounced shortly (3 hrs) after instillation. IOPIDINE 0.5% Ophthalmic Solution as a single therapy dosed TID for 90 days effectively lowered IOP by 3.9 to 7.9 mmHg in glaucoma patients. Although afternoon IOP reduction is comparable between a beta-blocker and IOPIDINE 0.5% Ophthalmic Solution, morning IOP reduction is not.

The IOP lowering efficacy of IOPIDINE 0.5% Ophthalmic Solution is diminished over time in some patients. This loss of control, or tachyphylaxis, appears to be an individual occurrence with an unpredictable onset.

Approximately one-fifth of patients treated with IOPIDINE 0.5% Ophthalmic Solution experienced apparent ocular allergic responses (mean onset time 38.6 days, with a range of 1 to 158 days), which resolved upon discontinuation of drug therapy.

The overall discontinuation rates in clinical studies with IOPIDINE 0.5% Ophthalmic Solution ranged from 14.8% in single therapy studies to 21.5% in adjunctive therapy studies.

The unpredictable loss of IOP control in some patients and incidence of ocular allergic responses and systemic side effects may limit the length of IOPIDINE 0.5% Ophthalmic Solution as a single, or adjunctive, medication for long term use. However, patients on maximally tolerated medical therapy still benefit from the additional IOP reduction provided by the short term use of IOPIDINE 0.5% Ophthalmic Solution.

Other Pharmacodynamic Effects:

Cardiovascular:

No clinically significant effects attributable to the drug could be found when blood pressure and heart rate were measured.

Central Nervous System Effects:

A decreased intraocular pressure was observed in the contralateral eye of normal volunteers treated unilaterally with 1% apraclonidine. During the seven hour period following treatment, there was a mean maximum decrease of 6.5 ± 4.3 mmHg in the treated eye (a $37.3\% \pm 20.4\%$ decrease from pre-treatment baseline) and a mean maximum decrease of 2.7 ± 3.4 mmHg in the contralateral eye (a $14.9\% \pm 19\%$ decrease from pre-treatment baseline).

Blood Flow Effects:

Apraclonidine Hydrochloride Ophthalmic Solution, because of its alpha adrenergic activity, is a vasoconstrictor. Single dose ocular blood flow studies in monkeys, using the microsphere technique, demonstrated a reduced blood flow for the anterior segment; however, no reduction in blood flow was observed in the posterior segment of the eye after a topical dose of 0.5% Apraclonidine Ophthalmic Solution. Chronic treatment of primates with 1.5% Apraclonidine Ophthalmic Solution three times a day for one year did not result in morphologic effects which would be indicative of vasoconstriction of the anterior or posterior segments of the eye. Ocular blood flow studies have not been conducted in humans.

Ocular Effects:

IOPIDINE 0.5% Ophthalmic Solution does not produce miosis or myopia commonly associated with cholinergic agents. The blurred vision and night blindness often observed with standard miotic therapy are not associated with IOPIDINE 0.5% Ophthalmic Solution. Thus patients with central lenticular opacities avoid the visual impairment caused by a constricted pupil.

Pharmacokinetics:

The onset of action of apraclonidine can usually be noted within one hour, and the maximum IOP reduction occurs three to five hours after application. Significant IOP reduction can be maintained with Apraclonidine 0.5% Ophthalmic Solution; duration of action in some patients is less than 12 hours.

Topical use of Apraclonidine Ophthalmic Solution 0.5% leads to systemic absorption. Studies of Apraclonidine Ophthalmic Solution 0.5% dosed one drop three times a day in both eyes for 10 days in normal volunteers yielded mean peak and trough concentrations of 0.9 ng/mL and 0.5 ng/mL, respectively. The half-life of Apraclonidine Ophthalmic Solution 0.5% was calculated to be 8 hours.

Studies in rabbits with radiolabeled apraclonidine have demonstrated absorption into the eye after topical ocular administration. In the iris-ciliary body, aqueous humor and lens, maximal concentrations were reached at approximately 2 hours after dosing (1.4, 0.5, and 0.2 ug equivalents/gm, respectively). The half-life in the aqueous humor was approximately 2 hours. Concentrations of 4.7 ug equivalents/gm were measured in the cornea at 20 minutes post-dose.

Topically administered apraclonidine is absorbed systemically and is present at low concentrations in the plasma. These data are consistent with the low frequency of systemic side effects observed with apraclonidine in controlled clinical studies. In humans, administration of IOPIDINE 0.5% Ophthalmic Solution three times per day for 10 days resulted in mean peak plasma concentrations of 0.9 ng/mL (ranging from not-detectable to 1.4 ng/mL). The plasma half-life was estimated to be 8 hours. Protein binding has been measured in human plasma by ultrafiltration and equilibrium dialysis (3). Both methods indicated the extent of binding to be low (22-29%).

Following IV administration, the plasma half-life of parent apraclonidine was 9 hours in the Cynomolgus monkey and 3 hours in the rat. In both species the half-life of radioactivity from ³H-apraclonidine was longer than that of parent drug. Approximately 10 metabolites were observed in rat urine and plasma. In both rats and Cynomolgus monkeys, urinary excretion was the primary route of elimination (65-75% of dose) with the balance eliminated in the feces.

Table 1
Incidence of Intraocular Pressure Spikes \geq 10 mm Hg

Study	Laser Procedure	Treatment			
		Apraclonidine		Placebo	
		N	%	N	%
1	Overall	0/76	0	22/79	27%
2	Overall	3/84	4%	15/84	18%
1	Trabeculoplasty	0/50	0	12/51	24%
2	Trabeculoplasty	2/41	5%	8/42	19%
1	Iridotomy	0/13	0	8/19	42%
2	Iridotomy	0/18	0	4/19	21%
1	Posterior Capsulotomy	0/8	0	2/9	22%
2	Posterior Capsulotomy	1/25	4%	3/23	13%

N = Number Spikes/Number Eyes

Table 2
Magnitude of Postsurgical Intraocular Pressure in Patients
with Severe Pressure Spikes \geq 10 mm Hg

Treatment	Total Spikes	Maximum Postsurgical Intraocular Pressure (mm Hg)			
		20-29 mmHg	30-39 mmHg	40-49 mmHg	> 50 mmHg
Apraclonidine	3	0	0	2	1
Placebo	37	3	21	6	7

TOXICOLOGY

Acute Toxicity:

The oral LD₅₀ of the drug ranged from 3 to 8 mg/kg in mice and 38 to 107 mg/kg in rats.

The intravenous LD₅₀ of the drug ranged from 6 to 9 mg/kg in mice and 9 to 21 mg/kg in rats.

LD₅₀ values in these ranges are indicative of a drug with a high degree of toxicity. Mortalities occurred one (1) to nine (9) days after administration, with systemic signs of toxicity including lethargy, impaired motor co-ordination and partial loss of consciousness. Bloody tears and/or urine and hypothermia were observed at extremely high doses (≥ 80 mg/kg).

Long Term Toxicity:

Topical ocular administration of two drops of 0.5, 1.0 and 1.5% Apraclonidine Hydrochloride Ophthalmic Solution to New Zealand albino rabbits three times daily for one month resulted in sporadic and transient instances of minimal corneal edema in the 1.5% group only. No histopathological changes were noted in those eyes. Topical ocular administration of 1.5% Apraclonidine Hydrochloride Ophthalmic Solution three times daily for one year to Cynomolgus monkeys elicited minimal conjunctival congestion and single instances of transient and sporadic fluorescein staining. No corneal cloudiness, iritis or lenticular changes were observed.

Reproduction and Teratology:

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses 5 to 10 times the maximum recommended human dose.

Teratogenicity studies with Apraclonidine HCl in rabbits and rats at doses up to 3.0 mg/kg/day in rabbits (60 times the maximum recommended human dose) and 0.3 mg/kg/day in rats (6 times the maximum recommended human dose) showed no evidence of fetal malformations, although embryotoxicity was evident at the high dose level in the rabbit study. Dose related maternal toxicity was evident in both the rat and rabbit studies.

Mutagenicity:

No evidence of apraclonidine-induced mutagenicity was seen with *in vitro* microbial (Ames test), mammalian (mouse lymphoma), chromosome aberration, sister chromatid exchange, or malignant transformation test assays or with *in vivo* micronucleus assay.

Carcinogenicity:

There was no significant increase in tumour incidence or type following two years of oral administration of apraclonidine HCl to rats at dose levels 20 times the maximum recommended human dose or in mice at dose levels 12 times the maximum recommended human dose.

Other Studies:

Two sensitization assays were performed in animals: the Buehler occlusive patch test in guinea pigs and the guinea pig maximization test (GPMT). While the Buehler test suggested little or no potential for sensitization, the GPMT revealed a moderate sensitization potential, indicating that there may be patients who develop a contact sensitization response with repeated use of this drug.

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